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IN INFANTS AND CHILDREN

FROM A STUDY OF
THE PLASMODIUM MALARÆ

BY
HENRY KOPLIK, M. D.

REPRINTED FROM
THE NEW YORK MEDICAL JOURNAL
FOR SEPTEMBER 16, 1893

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ERRATA.

Page 6, line 18, read : "I have *never* seen the quotidian parasite of Marchiafava and Celli ; and have seen the quartan parasite of Golgi but once."

Page 11, lines 3 and 4, for "melaniphorous" read "melaniferous."

MALARIAL FEVER IN INFANTS AND CHILDREN,
FROM A STUDY OF THE PLASMODIUM MALARIE.

THOUGH malarial fever in the adult has been one of the most favored themes of investigation in recent years, there is little or no work constructed upon modern data which treats of the disease as it occurs in children. The discovery of Laveran in 1880 and the immense field of knowledge opened up by it has not been utilized in the special field of diseases of children. It is difficult to account for this. The literature of malarial fevers and the *Plasmodium malarie* is too vast to attempt its review within the limits of this article, and such a review would serve no ulterior purpose. Laveran, Golgi, Marchiafava and Celli, Giuanieri, and in our country Osler, Councilman, and James, have drawn in their train no less than two hundred and fifty writers upon the *Plasmodium malarie*, as can be seen by consulting the literature recently collected by Mannaberg.

Mode of Investigation.—It has been the custom of the writer, in all cases of suspected or real malarial disease which have presented themselves in his practice within the past two years, to examine the blood with a view to making a diagnosis. In this way a large number of cases have been subjected to study and been proved to be not malarial infection, but various other diseases, with prognoses of slight to serious moment. Of this large material the cases which accompany the paper have been sifted. The temperatures, spleen, and general status have all been carefully noted. It was of interest to see how closely

certain infantile maladies could simulate malarial fever. The various methods of blood preparation—Laveran, Plehn, Marchiafava, and Celli—have been tried by the author. The following method was finally adopted as yielding uniform and invariable results: The blood in most cases was obtained from the finger tip by puncture; in exceptional cases from the spleen by means of a clean hypodermic exploring needle. The blood was examined when possible in a fresh condition by placing a drop on a slide, covering with a cover glass, and without a heated stage, studying under the microscope. This was followed as a diagnostic method, and in a busy dispensary or clinic is not always feasible. In such cases, where time is lacking, the blood is spread rapidly upon a dozen or eighteen cover slips by the Ehrlich method and with the forceps used by him for this purpose. The blood is allowed to dry in the air protected from dust. The blood is then placed upon the Ehrlich brass plate and heated for an hour or an hour and a half. The cover glasses are then stained in a very dilute solution of methylene-blue. Eosin is not used, as some varieties decolorize the blue and thus introduce an element of uncertainty. The above method has the advantage of simplicity, and with a little practice is easily attained and absolutely reliable. The blood is heated at the Ehrlich temperature above the boiling point on the plate (120° C.). The variety of dye is important; some blue does not stain. Grüber's powder blue, soluble in alcohol, is used. A few drops of the saturated solution in alcohol are added to an ounce of water. The cover glasses should not be deeply stained, as then certain pictures are lost. They are repeatedly washed in water and then dried without heat in the air. Heat decolorizes. By this method the blood cell is well hardened and its protoplasm and hæmoglobin stained more certainly than when hardened with alcohol, sublimate, or osmic acid. If desired, also part of the specimens may be stained by the Ehrlich anilin methods, to study other appearances, if present. The red blood-cells in malarial cases show the plasmodium in blue, the protoplasm as yellowish-green or colorless rings if anæmic, as the case may be. If the Ehrlich dyes are used—aurantia, orange G., etc., preferably the solution in glycerin of eosin, indulin, and

aurantia—the plasmodium does not stain, but the hæmoglobin of the red blood-cell is stained in shades of varying intensity.

Occurrence.—Of a very large number of cases examined by the writer for evidences of malaria in the blood which exhibited certain clinical signs, large spleen, an intermittent, remittent, or irregular temperature, anæmia, only a comparatively small number remain stamped by the blood appearances as malarial disease. This is the more interesting, as the methods of investigation were uniform and carefully carried out. In all the cases which were fixed by the blood examination to be malarial, a history of sojourn outside the city limits in the adjacent country districts could be easily obtained. Some of the cases contracted the disease in foreign lands. The manifestations of malaria in the American cases appeared shortly after the children had returned to the city. In only one case, in which the mother was a very intelligent German and the child aged nine years, the chills set in fully six months after the return to the city. In no case was there a history which could be verified by the study of the blood, etc., in which the malarial fever was contracted in this city. In this respect my observations agree with those of Dr. James, who in a very large series of adult cases failed to find malarial fever an indigenous or even sporadic disease in New York. My own material, ranking among the most extensive in this city, includes cases from all parts of the city, as well as that of the immediate vicinity of the dispensary. No less a clinician than Alonzo Clark, whose equal the city will rarely see, taught in his day that where the soil had been disturbed by excavations in the city streets, intermittent fever was apt to appear in adults. I have had sick children within the past few years from districts where extensive excavations were in progress, but in no case could I trace the malarial disease, if present, to this cause, or if thought to be present, it was excluded eventually by careful study. I conclude that there may have been a change in the subsoil of the city in recent years resulting from density of settlement and more perfected drainage. Malarial fever in children must be regarded as not indigenous in New York city to the extent formerly supposed.

Cases and Types.—The cases of malarial intermittent fever seen by the author range from ten months to nine years of age. Cases of very tender infancy may differ in manifestations from those of later childhood. But while many cases of later childhood resemble in every way those of adult life, yet in some older children this is scarcely so, and each case must be studied for itself. This study supports the view that in children and infants the manifestations of malarial poison are varied.

If the most recent text-books and articles treating of malarial fevers in children are consulted, it will be seen that the statement is invariably made that the type of fever in these subjects is quotidian, tertian, and quartan, in the frequency stated. The type of fever may, of course, vary with the locality and season of the year. I need but briefly refer to the quotidian parasite of Marchiafava and Celli and the tertian and quartan parasites of Golgi. In all my material, drawn from most removed spots, I have seen the quotidian parasite of Marchiafava and Celli and the quartan parasite of Golgi but once (Case XIV from Asia Minor). The investigations of Golgi are of such interest in this connection as to justify brief notice here. Golgi (*Fortschritte d. Med.*, 1889) concluded, from a study of endoglobular pictures, that the tertian and quartan types of intermittent fever were caused by two distinct species of plasmodia malariae. The one (tertian) ripens or runs its course in the red blood-cell in two days, the other (quartan) requiring three days for its full development and sporulation. In the parasite, therefore, he was able to recognize the type of fever, and even the time at which a chill was imminent. This latter was done by noting the stage of development of the parasite. In pure types of fever, either tertian or quartan, one generation of plasmodia, all in about the same stage of growth, would predominate. In those cases of tertian where the paroxysms were of daily occurrence, several generations of parasites, each with a different cycle of development, were found in the blood. The same was true of irregular types of fever with the tertian parasite. The same argument could be applied to the quartan fevers. If more than one generation of parasite existed in the blood in a tertian case, the fever could become quotidian with

daily paroxysms due to the ripening of distinct sets of parasites on different days, each set of parasites taking forty-eight hours to mature; thus 1 0 1 0 1 0 1 0 1—pure tertian, one parasite; 1 2 1 2 1 2 1 2 1—double tertian, two parasites, giving quotidian paroxysms.

In quartan we may have the following combinations: 1 0 0 1 0 0 1 0 0 1 0 0 1—pure quartan, one parasite; 1 2 0 1 2 0 1 2 0 1 2 0 1—double quartan, two parasites; 1 2 3 1 2 3 1 2 3 1 2 3 1—triple quartan, three parasites, giving quotidian chills (Mannaberg).

It will be seen that no quartan combination of parasites can cause pure tertian types of paroxysms, though we may have quotidian chills, and in this respect it may resemble the tertian fever.

Marchiafava and Celli described a mild quotidian type of fever as caused at least in the district studied by them by a small parasite with very little pigment. James found most of his cases in the first thirty examined and published by him to be tertian types caused by the tertian parasite. He had never met the quartan parasite and its type of fever. All the writer's cases in children, with the exception of two, were marked by the presence of the tertian parasite. One of the exceptional cases had lasted some time, Russian in origin, and the blood showed the half-moons and crescents of Laveran; rarely was a full tertian parasite found. The other case was a quartan intermittent containing in the blood the quartan parasite of Golgi. My material places the tertian fever as first in frequency. It must be remembered that in tertian cases quotidian or daily paroxysms occur. This was so in several of my cases. The older authors, in placing the quotidian type of paroxysm as first in frequency (Hench), were correct as to occurrence of paroxysms, but not really correct as to nomenclature of the fever, for it will be seen they may have had the tertian parasite to deal with. It is also possible that in many of these cases the daily paroxysms did not occur at the same time exactly if such had been noted.

The Plasmodium Malariae.—It is not intended to give a description of the *Plasmodium malariae* here, as this has been well done by others, but merely to point out, as has

been done above, that the various types of fever (tertian, quartan, quotidian) may be caused by distinct species of parasites differing decidedly in properties (mild, malignant) from each other. The doctrines promulgated by Golgi and his followers differ from those of Laveran, who thought that all intermittent or malarial fevers were caused by the same parasite, which was polymorph and varied in its manifestations in different spots and individuals. In children the writer has observed that it is quite common to obtain a history showing that the paroxysms at first were purely tertian; after a time the little patients would develop double tertian, or what the older authors called quotidian chills. In these cases the chills occur at the same hours, only every other day, or the chill of one day is not of the same series as that of the day immediately following, but removed by one day (two sets of parasites). Frequently we will obtain a history of pure tertian chills every second day at the same hour. If many of such children are examined on the day on which they are supposed to be exempt from fever, it will be observed that they will exhibit a very mild febrile movement, half or three quarters to one degree above the normal in the rectum (Case XII). On closely questioning the parents or patient, it will be found that on these days at a certain hour the children complained of lassitude or headaches. If the blood of these children is examined in the interval, the parasites will be found in varied stages of development. We have here to deal with a form of double tertian fever in which either one set of parasites runs an abortive course of development and sporulation or, when sporulation occurs, it is not sufficiently abundant to cause a chill. The temperature in such cases can be remittent in curve. Though at first parasites may exist in the blood in one generation giving pure tertian, we are impressed, after a study of these cases, that these pure types give way to double tertian fevers after having lasted a short time. In quotidian paroxysms of chills and fever we must be prepared to meet the tertian parasite in children. Further study in other districts will decide how frequently, if at all, the quotidian parasite of Marchiafava and Celli is found in children in this country. The quartan parasite also needs further study in children.

Condition of the Blood ; Tertian Parasite.—In pure tertian fever of recent development (Case XV) an examination of the blood a few hours after the chill showed almost exclusively young spore forms in shape of non-pigmented rings in red blood-cells only ; rarely was a fully developed plasmodium, apparently delayed in sporulation, found. In some specimens groups of sporula were found free. We can theorize that the delayed form might in time become the leader of a separate generation of parasites. In double tertians, examined between the paroxysms, forms of plasmodia in varied stages of development were found. For convenience they are grouped—

A. The colorless, irregularly oval-shaped plasmodium, without pigment, having a rapid amœboid movement.

B. The same bodies as A, but larger, containing rods and fine pigment granules. The rods and granules were fine, resembling minute bacilli, having with the amœboid movement of the plasmodium a rapid oscillatory motion, at times aggregating toward the center of the plasmodium, at others collecting at the periphery. Some granules finally arranged as broken rings in the plasmodium. In this young plasmodium the red blood-cell envelope could be made out.

C. Full-developed plasmodium having structure same as above but larger.

D. White blood-cells, varied in shape, having within their cell body granules and rods of pigment (melaniferous leucocytes). These white blood-cells were not seen to perceptibly change form (without heated stage).

F. Rarely small round spherical bodies with the so-called flagella were found. Only met in two cases.

Stained Specimens contained : A. Hyaline bluish-stained bodies, ring-shaped, inside the red blood-cell. They contained generally at the periphery a darker speck, the nucleus (young native forms).

B. Older forms, bluish-stained, irregular-shaped, no pigment.

C. More advanced forms shaped like a crescent, the points of the crescent inclosing a hyaline, structureless, spherical mass (nucleus), the body of the crescent just showing the indications of pigment. The red blood-cell *distinctly swollen* above normal size.

D. More advanced forms with or without nucleus, sometimes with vacuoles or empty openings which did not stain; pigment more abundant. Red blood-cell easily made out as anæmic ring, much swollen above normal size.

C. Fully developed plasmodium ready to sporulate; pigment dividing the plasmodium into districts; at other times this not found.

E. Free groups of sporula (after a chill).

F. Spherical hyaline bodies with flagella, rare in dried specimens; found only twice in fifteen cases.

G. White blood-cells containing pigment.

H. Red blood-cells with irregular bluish streaks.

I. Red blood-cells which stained slightly blue and were dotted with bluish specks.

The half-moons of Laveran were found in three cases of tertian accompanying the regular parasite. In a fourth case they were found in the blood only after the same had been repeatedly examined by stain. This was a chronic case and should teach that in these cases where the crescents and moons are found almost exclusively the blood must be repeatedly examined. They have, as we know, in adults persisted a long time into convalescence (Laveran, Mannaberg).

The Ehrlich method does not stain the plasmodium, but it demonstrates very clearly the anæmia of the red blood-cell and its lack of hæmoglobin in proportion to the amount of pigment contained. The larger the plasmodium and the more pigment, the more anæmic the erythrocyte. *Nucleated red* blood-cells were found in two cases in which the anæmia was profound. Eosinophile cells were in some cases so few as to be found with difficulty; in others they were more numerous. In no case increased. The multinuclear leucocytes seemed to be the predominating form of white blood-cell. The case of quartan fever coming under my observation contracted the fever in Asia Minor, where the patient was born. The fresh blood, examined in the intervals of the chills, showed, with a temperature of 99·8° F. in the rectum—

A. Free granules of pigment in the blood, larger than in the tertian cases and irregular in shape. The pigment sometimes found alongside of transparent small round

bodies or spores. Sometimes fibrin threads started from the pigment.

B. White blood-cells containing pigment (melaniphorous leucocytes).

C. The colorless plasmodium inside the red blood-cell, having a slowly changing movement.

D. Peculiar brassy-colored shrunken red blood-cells with a small mass of pigment at one spot.

E. Fully developed parasites, the exact counterpart of the photographs published by Golgi of the quartan parasite (*Zeitsch. f. Hygiene*, Bd. x, Heft 1), not seen by me in any of my tertian cases. The "daisy-shaped" forms. The pigment in form of a dark-brown central mass, irregular and large. The finer pigment rods and granules of the tertian forms not seen.

The figures (microphotographs) show the *Plasmodium malariae* of the tertian variety in various stages of development in the same specimen of blood. Taken in the interval of the chills.

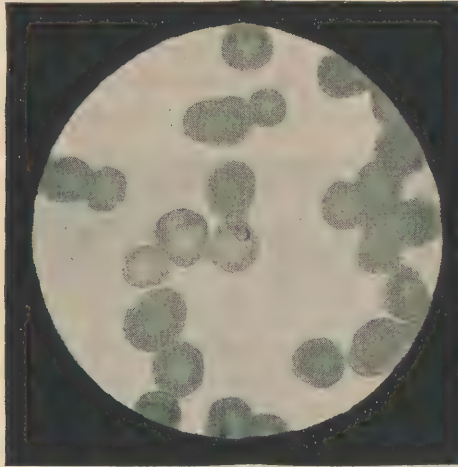


FIG. 1.—Young native parasite inside red blood-cell with nucleus, no pigment. $\times 1,000$. Ehrlich dried specimen stained with methyl-blue. Zeiss immers. $\frac{1}{25}$, projec. ocular 4. Calcium light.

Clinical Course.—It is intended only to touch upon those points which appeared of interest in the author's cases as having been accompanied by the *Plasmodium malariae* in the blood of the patients.

Incubation Stage.—Some children while living in a malarious district do not manifest any of the classical

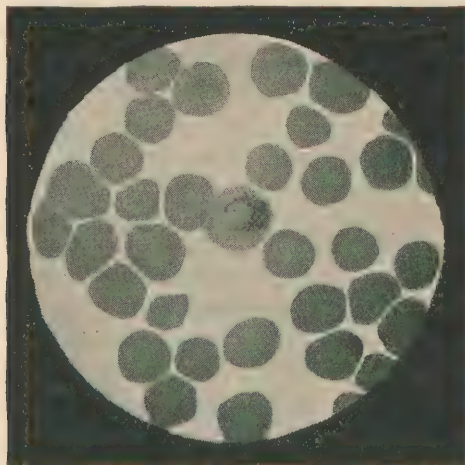


FIG. 2.—Young parasite inside swollen red blood-cell, the tips of the crescent holding the hyaline nucleus. $\times 1,000$. Same as above in stain and preparation.

symptoms of malarial fever. At first there are absolutely no objective signs. The febrile movement must be low, coupled with a slight anæmia not noticeable at first to the

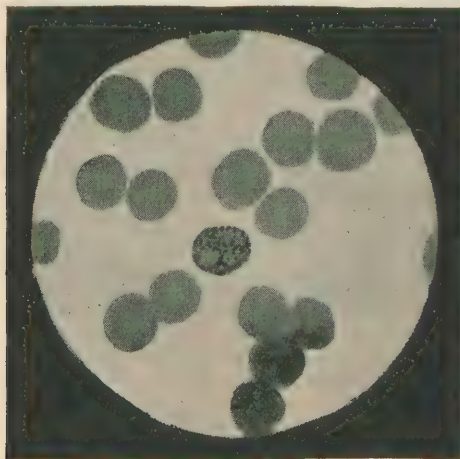


FIG. 3.—Fully developed parasite, rods of pigment arranged in round areas, nucleus indicated by opening, also vacuoles. $\times 1,000$. Stain, preparation, and lens as above.

parents. After coming away from the infected district the chills appeared in some of my cases in from eleven days to two to four weeks. Close questioning failed to discover illness of a marked character while at the malarial spots. In one case, in which the mother and the patient, nine years old, both were intelligent, the chills appeared fully six months after leaving the infectious district. Here the incubation may have been prolonged, or, what is more probable, the poison may have manifested itself months previous in the form of masked symptoms since forgotten.

Chills.—In one case my attention was called to an infant, aged ten months, whose sister was under my care for malaria. The infant was extremely anæmic. There was no regular febrile curve, and at no time were there chills. The spleen was large. The parents had noticed the pallor, but had not considered the infant ill, and did not ask advice about its condition. The *Plasmodium malariae* was found in the blood abundant and in various phases of development.

In another infant the chills manifested themselves in a blueness and coldness of the surface coming on at a certain hour of the day. This was followed by a febrile movement and sweats. In another case, a grown boy, the paroxysms were sometimes indicated by headache and lassitude coming on at a certain hour.

Typical chills were present in most cases. In no case was there eclampsia.

Fever.—I have elsewhere called attention to a set of cases in which the pure tertian paroxysms are accompanied by a low grade of continued fever on the day upon which the patient is supposed to be exempt. On this day, at a certain hour, lassitude and headache will indicate the duplicate chill. The temperature upon these days, even in the rectum, is only slightly raised—a half to one degree. It seems as though in these cases we have a marked attack of intermittent alternating with the classical paroxysm.

Spleen.—In all but one case the spleen was larger than normal, and could be palpated below the border of the ribs. In the case in which the writer found only oval and crescent-shaped forms of plasmodia the size of the spleen was enormous. This was a chronic case. In the case in

which the spleen was not felt *below* or *behind* the ribs (Case XV) it could be mapped out by percussion. In this case, in which the patient was seen on the first day of the paroxysms, the spleen was not at all as large as we find it in children. Here the difficulties of diagnosis would be increased by an omission of a blood examination. At this early day, without perceptible enlargement of the spleen, the *Plasmodium malarie* was found in the blood.

Anæmia, which was present in most cases, persisted for a long time after the spleen could not be felt below the border of the ribs.

Repeated Attacks and Relapses.—A few of my cases suffered from a number of attacks of intermittent before coming under observation. In these cases, notably the quartan case, the anæmia was not very profound, nor was the spleen markedly larger than in those cases in which there was a history of a single attack alone. Children thus seem to bear the malarial poison well in certain districts, and must be long sufferers before exhibiting profound effects. What the parents call a number of attacks are legitimately assumed to be relapses. Excluding two cases, including the quartan case, many cases acted thus: The parents, after having dosed the children with quinine, noted the disappearance of the paroxysms and suspended treatment. In such cases the chills would return after an interval. How long this interval can be may be seen from the following well-observed case: An infant, aged fifteen months, was treated by me for malarial fever, and the treatment continued until not only the chills disappeared and the spleen returned to the normal, but arsenic was administered for a long period until all anæmia had disappeared. The infant was seen at intervals, and continued healthy. Fully nine months after the original attack, without having returned to the malarious district, the infant became anæmic and manifested tertian paroxysms, with the reappearance in the blood of the plasmodium. Such cases can only be explained by assuming the long resistance of spores to the action of quinine and arsenic. Laveran and Mannaberg found crescents in the blood long after convalescence was established.

Differential Diagnosis.—The study of the blood and

allied diseases, especially in infancy and childhood, has advanced so much within the past decade that the diagnosis of malarial disease to-day presupposes an intimate knowledge of the diseases of the blood and spleen as well. The enlargement of the spleen, upon which so much stress was formerly laid, is present in malarial poisoning it is true, but it has been shown in Case XV to be absent at least at the outset of the malady. Enlargement of the spleen is also present in other diseases in which there are remittent curves of temperature, such as typhoid fever and chronic enterocolitis. In rhachitis we find a number of cases with enlarged spleens which are apt to exhibit transient temperatures due to dyspepsias. Severe chronic anæmias, with or without rhachitis, show large spleens. I need only refer to that interesting condition of infancy known as anæmia infantum, pseudo-leucæmia, or von Jaksch's disease, examples of which have been recently published by the writer in the *Archives of Pædiatrics*. In one of these cases, which is still alive and doing well after a year of observation, the enlarged spleen was combined with a remittent curve of temperature. The author has met cases of the infectious fevers, such as varicella, which at the outset give a history of repeated chills and show enlarged spleen. Cases of congenital syphilis will at times show not only an enlarged spleen, but enlarged liver also, and this in cases which have been observed from birth. It seems to the author that in addition to our history we must examine the blood in each case for a crucial exclusion diagnosis. In cases of marked intermittent fevers, obscure symptoms (*intermittens larvata*), such as have been published by Filatow, examination of the blood gives us the only crucial test. The cases in which a negative result is obtained and in which the plasmodium is difficult of discovery are chronic cases with a continued remittent or irregular temperature curve; here the plasmodium appears mostly as half-moons and crescents of Laveran, and many specimens of blood may be examined without their discovery, such as Case IV. Quinine administered in even moderate doses will drive the plasmodium out of the circulation in children even after twenty-four hours of exhibition of the drug. With correct technique and the observance of the above precautions it is difficult to conceive of negative cases.

Epitome of Cases.

Case.	Age.	Sex.	Number of the attack.	Duration of attack.	Presence or absence of chill.	Type of paroxysm.	Species of parasite.	Spleen.
I.	9 years.	Female.	First.	2 weeks.	No chill.	No type; irregular.	Tertian.	Large.
II.	15 months.	Female.	First.	3 weeks.	Yes.	At first tertian, now quotidian.	Tertian.	Large.
III.	10 months.	Female.	First.	?	None.	Irregular.	Tertian.	Large.
IV.	3 years.	Female.	First.	4 months.	None.	Irregular.	Crescents and tertian.	Very large.
V.	8 years.	Female.	First.	3 months.	Yes.	Tertian.	Large.
VI.	9 years.	Male.	First.	10 days.	Yes.	Tertian.	Tertian.	Large.
VII.	6 years.	Female.	First.	Yes.	Tertian.	Tertian.	Large.
VIII.	22 months.	Male.	First.	7 days.	None.	Quotidian or double tertian.	Tertian.	Large.
IX.	5 years.	Male.	Second.	3 days.	Yes.	Tertian.	Tertian.	Large.
X.	4 years.	Female.	First.	3 weeks.	Yes.	Tertian.	Tertian.	Large.
XI.	3½ years.	Male.	Second.	2 months.	None.	Pure tertian.	Pure tertian.	Very large.
XII.	9 years.	Female.	First.	5 days.	Chill only every other day; fever on the day intervening.	Double tertian; an attack not accompanied by a regular chill.	Tertian.	Large.
XIII.	8 years.	Female.	First.	4 weeks.	Yes.	Double quartan.	Tertian.	Large.
XIV.	5 years.	Male.	Several.	weeks.	Yes.	Double quartan.	Quartan.	Large.
XV.	3½ years.	Female.	First.	12 days.	Yes.	Tertian.	Tertian.	Normal in size.

NOTE.—Case XII, on the day when patient was supposed to be well, temperature 101.2° in rectum (marked attack without chill).

Treatment.—The mode of treatment of intermittent fevers adopted by me is simple and will scarcely present anything novel.

Quinine in the form of the bisulphate or hydrochloride is the most favorite prescription. Children will bear larger doses than adults and should have it thus. The paroxysms are anticipated by two hours by the first dose, and the second dose is given at the time of the paroxysm; thus the drug is exhibited only twice daily. Quinine will eliminate the paroxysms, but in some children improvement ceases there, and arsenic, in the form of Fowler's solution, must be administered with the quinine. After the spleen ceases to be felt below the border of the ribs quinine is stopped and arsenic is continued until all signs of anæmia have disappeared; this, in some cases, is quite an extended period of time. Inasmuch as in children preparations of iron are not so well borne and the intestinal processes are much disturbed by its exhibition, it should be withheld. If exhibited at all for the anæmia, it should be done through the agency of the vegetable preparations, the mannitate, or those preparations which contain minimal quantities of manganese.

THE New York Medical Journal.

A WEEKLY REVIEW OF MEDICINE.

EDITED BY

FRANK P. FOSTER, M.D.

THE PHYSICIAN who would keep abreast with the advances in medical science must read a *live* weekly medical journal, in which scientific facts are presented in a clear manner; one for which the articles are written by men of learning, and by those who are good and accurate observers; a journal that is stripped of every feature irrelevant to medical science, and gives evidence of being carefully and conscientiously edited; one that bears upon every page the stamp of desire to elevate the standard of the profession of medicine. Such a journal fulfills its mission—that of educator—to the highest degree, for not only does it inform its readers of all that is new in theory and practice, but, by means of its correct editing, instructs them in the very important yet much-neglected art of expressing their thoughts and ideas in a clear and correct manner. Too much stress can not be laid upon this feature, so utterly ignored by the “average” medical periodical.

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